Support for new claims 98-103, 106-109, 111-117, 120-123, and 132 is found in original claims 20-39.

In the Advisory Action, the comments concerning the previously submitted Abstract are not understood; the submitted Abstract *is* on a separate page and *does* comprise a single paragraph. A copy of the previously submitted Abstract (filed June 10, 2001) is attached hereto.

The "new matter" objection contained in the final Office action (mailed 12-18-00) is deemed withdrawn since it is not repeated in the Advisory Action.

The Advisory Action maintained the rejection of claims under 35 USC 103(a) based on the teachings of WO 95/05849 ("Mouritsen") combined with *Nature, 312*, 724-729, 1984 ("Pennica"), *Nature, 313*, 803-806, 1985 ("Shirai"), *Science 228*, 149-154, 1985 ("Wang"), "Crystal structure of TNF," *Tumor Necrosis Factors, Structure, Function, and Mechanism of Action*, Ch. 5, 93-127, New York, 1992 ("Jones"), and *Eur. J. Immunol, 19*, 2237-2242, 1989 ("Panina-Bordignon"). Reconsideration is requested in view of the new, replacement claims submitted hereby.

It is noted that the rejection under § 103(a) implicitly acknowledges novelty of the subject matter of claims 50-76, now cancelled. As the scope of the corresponding new claims is clarified/limited compared to claims 50-76, novelty is maintained.

With respect to the obviousness rejection under §103(a), the statement of rejection is incorrect in concluding that the skilled person would have arrived at the presently claimed invention without need of an unobvious step, merely by selecting modified proteins capable of inducing autoantibodies in humans in the same manner as taught in Mouritsen. Such conclusion is the result of hindsight reasoning. "One cannot use hindsight reconstruction to pick and choose among isolated

disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Without the teachings of the presently claimed invention, one would never have arrived at the claimed invention from the teaching of Mouritsen, alone, or in combination with the cited secondary references..

What Mouritsen teaches or suggests to one skilled in the art begins with what the references, expressly, discloses. Mouritsen states that the invention disclosed therein is a method for utilizing the immune apparatus to remove and/or down-regulate self-proteins, proteins that may cause diseases, or symptoms or signs of diseases (page 1). Examples of such self-proteins are IgE, TNF-alpha and hormones (page 2). It is stated that the antibody response was expected to be MHC restricted, but it turned out not to be restricted in the immunized mice used, to the surprise of the inventors (page 5). The reason for this is not clear to the inventors, and more explanations are discussed without a conclusive thesis (pages 5-6). At the bottom of page 6, it is stated that the Mouritsen invention concerns the surprising effect that recombinant modulated proteins, with insertions of one or more foreign T cell epitopes, induce autoantibodies against the proteins. It is further stated that the antibody response is not necessarily restricted to the inserted T cell epitope. T cell epitopes having a length of 12-15 amino acids were inserted in ubiquitin and murine TNF-alpha (page 7). On page 7 it is stated that by using the principle of inserting T cell epitopes, the risk of inducing allergic side-effects may be reduced and TNF-alpha may be detoxified by simultaneously removing or mutating biologically active protein segments. The autovaccine could be against TNF-alpha or gamma-interferon for treatment of patients with cachexia, e.g., cancer patients, against IgE

for the treatment of allergy, or against TNF-alpha, TNF-beta or interleukin 1 for the treatment of patients with chronic inflammatory diseases (page 7-8).

Example 1, page 8, of Mouritsen discloses a method of inserting a T cell epitope in ubiquitin. Example 2, page 8-9, discloses a method of inducing antibodies in mice against ubiquitin by the use of two different recombinant ubiquitin molecules comprising different T cell epitopes (which are also different from the epitope inserted in Example 1). It is not clear whether the ubiquitin is murine or of any other origin, such as human.

Example 3, page 10-12, of Mouritsen discloses induction of autoantibodies against murine TNF-alpha. Three mutants of the murine TNF-alpha protein, MR101, were obtained for immunization. MR103 comprises an ovalbumin H-2^d restricted insert, which replaces amino acids 26-35 in the MR101. MR105 comprises a hen eggwhite lysozyme H-2^k restricted insert, replacing amino acids 5-20 in MR101. MR106 comprises the same H-2^k restricted insert as in MR105, replacing amino acids 126-140 in MR101. The mutants were made by different techniques. MHC haplotype H-2^d and H-2^k mice were immunized with MR103 and MR106 emulsified in Freunds' complete adjuvant. All mice showed antibody response against biologically active MR101 in an ELISA method. Control mice were immunized with MR101 and PBS, respectively, and showed no antibody reactivity. It is not clear whether an adjuvant was used. The response was not MHC restricted according to the implanted T cell epitopes. Mouritsen concludes (page 7):

> Taken together these results illustrate (a) the ability of the method of the invention to induce autoantibodies towards a secreted autoprotein and (b) the improved efficiency of the herein described method with regard to inducing a response in a

broader MHC population than predicted by the MHC binding ability of the inserted T cell epitopes.

Example 4, page 12, of Mouritsen discloses a comparison of the induction of autoantibodies in MHC haplotype H-2^k mice (C3H) against murine TNF-alpha by immunization with MR105 emulsified in Freunds' complete adjuvant and MR101 conjugated to E. coli proteins. The E. coli proteins are not defined. No adjuvant seems to be used with the conjugate. It is stated that MR105 is biologically inactive as judged by the L929 bioassay for TNF-alpha. Both groups of immunization resulted in induction of autoantibodies; however, the response against MR105 was earlier and stronger.

Example 5, page 12-14, of Mouritsen discloses an experiment set up for explaining the reason for the observed non-MHC restricted autoantibodies. Different peptides are inserted in ubiquitin. The experiment does not lead to any conclusion.

Example 6, page 14-15, of Mouritsen speculates in ways of treating diabetes and inflammatory diseases: Genes coding for TNF-alpha should be modified by insertion of appropriate segments coding for T cell epitopes derived from e.g. tetanus toxin or influenza hemagglutinin. The genes are expressed and the recombinant TNF-alpha purified. The recombinant proteins may be coupled to immunologically active cytokines. The recombinant proteins are proposed to be formulated with appropriate adjuvants and administered as anti-TNF-alpha vaccine to patients suffering from diseases where TNF-alpha is important for the pathogenesis. As examples of such diseases are mentioned diseases where TNF-alpha is believed to play an important role in chronic inflammatory diseases such as rheumatoid arthritis, in cachectic conditions seen in cancer patients

and in patients with chronic infectious diseases such as AIDS. It is further mentioned that TNF-alpha plays a role in septic shock and in the development of type II diabetes mellitus.

Claim 1 of Mouritsen concerns a method for modulation of self-proteins by inducing antibody responses against such proteins wherein one or more foreign T cell epitopes are inserted in the proteins by molecular biological means in order to render said proteins immunogenic. The claim thus concerns a method of treatment.

Claim 2 of Mouritsen recites that immunodominant T cell epitopes from tetanus toxoid or diphtheria toxoid are inserted in the proteins. No working examples support this. Only tetanus toxin is mentioned in Example 6.

Claim 3 of Mouritsen concerns an autovaccine against undesirable proteins in humans or animals, which vaccine consists of one or more self-proteins modulated according to claims 1 or 2 and formulated with pharmaceutically acceptable adjuvants, such as calcium phosphate, saponin, quil A and biodegradable polymers. According to the use of the wording "self-proteins modulated according to claim 1 or 2", the self-proteins of the vaccine are unmodified, as it is native self-proteins that are modulated in the method of claims 1 and 2. The pharmaceutical adjuvants mentioned are not supported by working examples.

Claim 4 of Mouritsen recites that the modulated self-proteins are prepared as fusion proteins with suitable, immunologically active cytokines. There are no working examples.

Claim 5 of Mouritsen recites that the autovaccine is against TNF-alpha or gamma-interferon for treatment of patients with cachexia. Working examples 3 and 4 show an induction of antibodies in mice against murine TNF-alpha.

Claim 6 of Mouritsen recites that the autovaccine is against IgE for the treatment of patients with allergy. No working examples.

Claim 7 of Mouritsen recites that the autovaccine is against TNF-alpha, TNF-beta or interleukin 1 for treatment of patients with chronic inflammatory diseases. Working examples 3 and 4 show an induction of antibodies in mice against murine TNF-alpha.

Claim 8 of Mouritsen recites that the autovaccine is against TNF-alpha, TNF-beta or interleukin 1 for treatment of patients with rheumatoid arthritis or inflammatory bowel disease. Working examples 3 and 4 show an induction of antibodies in mice against murine TNF-alpha.

Claim 9 of Mouritsen recites that the autovaccine is against TNF-alpha for treatment of diabetes mellitus. Working examples 3 and 4 show an induction of antibodies in mice against murine TNF-alpha.

The teachings of Mouritsen can be viewed as a thesis, documented in the description, especially in the working examples. The teachings may also lead the skilled person to understand and use the Mouritsen invention and what can be directly or indirectly deduced therefrom, without involving any non-obvious steps. Speculation, without any support, is not a teaching or suggestion of obviousness to one skilled in the art, but merely an invitation to experiment, i.e., "the rather general urge commonly felt by alert research men to investigate each new . . . process that appears

in order to see if it can be used to improve any of the processes in which they are currently interested." *Ex parte Polak*, 83 USPQ 135, 136-137 (POBdApp 1949).

Hence, in Mouritsen, the thesis is that self-proteins may be modulated by antibody responses against such self-proteins, the antibodies being induced by self-proteins, wherein one or more foreign T cell epitopes have been inserted by molecular biological means. The T cell epitopes may be immunodominant epitopes from tetanus or diphtheria toxoid. The self-proteins may be TNF-alpha, TNF-beta, gamma-interferon, interleukin , or IgE, and the diseases to be treated may be cachexia, e.g., in cancer patients, chronic inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease, diabetes mellitus, or allergy. The description supports an induction of antibodies against ubiquitin and murine TNF-alpha in mice, using T cell epitopes from albumin and hen eggwhite lysozyme. The antibodies raised in the 2 strains of mice turned out not to be MHC restricted in accordance with the T cell epitopes used. This is surprising to the inventors and cannot be explained. Thus, no teaching can be drawn from this information in itself. It is further stated in the description that toxic self-proteins such as TNF-alpha can simultaneously be detoxified by removing or mutating biologically active protein segments. For the modified TNF-alpha molecules MR103 and MR106 no such removal or mutation is disclosed. The biological activity of MR103 and MR106 is neither reported nor tested. On the other hand, MR105 is reported to be biologically inactive, apparently due to the insertion of the T cell epitope. Mouritsen does not teach any general method of obtaining biologically inactive self-proteins.

Thus, Mouritsen teaches a general approach and provides examples of modified ubiquitin and TNF-alpha molecules and their use in inducing autoantibodies in mice. Further, Mouritsen speculates that this teaching may be extended to any induction of antibodies against any self-proteins in any animal or human.

As to what Mouritsen teaches about inducing autoantibodies against TNF-alpha in humans, the reference discloses that one or more T-cell epitopes should be introduced into the human TNF-alpha molecule. It does not teach where to introduce the foreign epitope, or that there might be preferred parts for the insertion. It further teaches that TNF-alpha, as a toxic self-protein, could be detoxified by simultaneously removing or mutating biologically active segments. It does not teach where such segments are situated, how they could be identified, or how they should be removed/mutated in addition to the insertion of foreign T cell epitopes. It also teaches that T cell epitopes from tetanus and diphtheria toxoid might be used, however, without any support for the usability for such epitopes in mice and/or human TNF-alpha.

Using the specific examples in Mouritsen, as an indication of useful TNF-alpha segments as target for modifications, the three segments MR103, MR105 and MR106 might be selected. However, if the problem is posed that the modified TNF-alpha should be devoid of native biological activity for use in humans, MR105 is the most attractive – or only one possible – as the modification in MR105 leads on its own to inactivation of the biological activity. Modifications as in MR103 and MR106 would leave the skilled person with the additional problem of looking for targets for an inactivation of the biologically activity. Therefore, with the objective of obtaining modified TNF-

alpha molecules devoid of biological activity for use in inducing autoantibodies in humans, Mouritsen only points to a modification in a segment such as in MR105. However, by introducing a T cell epitope different to the hen eggwhite lysozyme used in MR105, the result is a long way from given. As indicated on page 6 of Mouritsen, the inserted peptide should minimally obscure the tertiary structure of the self-protein. Further, the stated advantageous lack of MHC restriction could by no means be expected when using other T cell epitopes.

In MR105, a modification of amino acids 5-20 in the mouse TNF-alpha molecule leads to an alleged inactivation of the biological activity and induction of antibodies in mice. Amino acids 5-20 comprise the entire B strand of the back beta-sheet. A similar modification of the human TNF-alpha is reported in the present patent application, namely the molecule denominated TNF2-1, which has a modification of amino acids 10-25, apparently, including the entire B strand of the back beta sheet. TNF2-1 is proved to be unable to induce antibodies against human TNF-alpha. Thus, the only specific teaching one might deduce from Mouritsen concerning modification of human TNF-alpha has turned out to be misleading. Such a modification does not lead to the result one could hope for. A seek-and-find solution to the present problem posed, necessary to effect obviousness following the reasoning contained in the statement of rejection, does not amount to obviousness under §103(a) but, at best, provides an obvious suggestion to experiment, i.e., "the rather general urge commonly felt by alert research men to investigate each new . . . process that appears in order to see if it can be used to improve any of the processes in which they are currently interested." *Polak*, 83 USPQ at 36-137. "Obvious to experiment" is not the standard for obviousness under §103(a); "selective

hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings." *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988). Moreover, a seek-and-find solution to the present problem posed would fail at the first attempt, thus, discouraging the skilled person from following this strategy.

Modifications in the human TNF-alpha molecule reported in accordance with the presently claimed invention, have shown how very important it is to select the segments to be modified. Furthermore, only in accordance with the presently claimed invention are there obtained modified TNF-alpha molecules that are able to induce autoantigens and, at the same time, are devoid of biological activity, due to the replacement of a native segment,.

Therefore, Mouritsen is fatally deficient in providing teachings that, when combined with the teachings of the secondary references relied on in the statement of rejection, would have allegedly rendered the presently claimed invention obvious under §103(a). In fact, any combination with background knowledge about the site for biological activity would lead away from the presently claimed invention.

As can be seen from the above explanation, it is clear that Mouritsen discloses a general idea of how to modulate unwanted actions of self-proteins by using such self-proteins modified by foreign T cell epitopes to induce autoantibodies to the self-proteins. Mouritsen does not, however, teach the existence of individual differences in different self-antibodies, even in closely related self-proteins, such as murine and human TNF-alpha. Thus, the presently claimed invention may be seen as a selection of individual properties and restrictions to be used in connection with the development of

autoantibodies to the human TNF-alpha molecule. Such properties and restrictions can only be judged as obvious in hindsight.

The secondary references relied on to reject the claims add nothing to cure the fatal deficiencies of Mouritsen, as explained above. Accordingly, the present claims are patentable under §103(a) and the rejection of record should be withdrawn.

Favorable action is therefore requested.

Respectfully submitted,

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Date: March 4, 2002
HBJ:WEP/rdt
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1-8-02 TC 1-9-02 Christy P60953US1

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/060,294	04/15/1998	MARTIN ROLAND JENSEN	P60953US1	9443

7590 01/03/2002

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/03/2002

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